Environmental Health Perspectives
Vol. 21, pp. 7–16, 1977

Carcinogenicity Studies on Halogenated Hydrocarbons

by Elizabeth K. Weisburger*

A series of halogenated compounds was tested by oral intubation in 200 Osborne-Mendel rats and 200 B6C3F1 mice of both sexes. Carbon tetrachloride, used as a positive control, induced liver and adrenal tumors in mice and neoplastic nodules in the livers of rats. 1,2-Dibromoethane and 1,2-dibromo-3-chloropropane caused stomach tumors with many metastases in both rats and mice. Chloroform, known to cause hepatocellular carcinomas in mice, led in addition to kidney tumors in male rats. 1,2-Dichloroethane was much weaker than the analog, 1,2-dibromoethane, and induced only a few stomach tumors in rats. It increased liver and lung tumors in mice. Most of the compounds, namely, trichloroethylene, 1,1-dichloroethane, 1,1,2-trichloroethane, hexachloroethane, and tetrachloroethylene, increased hepatocellular carcinomas in mice but had little or no action in rats. Iodoform tended to increase thyroid tumors in male rats and hepatocellular carcinomas in male mice. The action of 3-chloropropene was questionable. No tumors could be attributed to 1,1,1-trichloroethane (methylchloroform).

Introduction

In the 1960's, scientists associated with the Bioassay Program of NCI realized that although many halogenated aliphatic compounds had widespread environmental uses, they had not received adequate chronic toxicity studies. Furthermore, at that time there were fewer regulations on such substances since they apparently did not fall in the province of the FDA, then almost the sole agency involved with such matters. Therefore when the opportunity arose to test chemicals under the contract system, a study of halogenated compounds with varied uses was initiated.

Materials and Methods

Chemicals

The chemicals were generally purchased from laboratory supply houses. Purity of each was checked by gas chromatography and infrared spectroscopy. Gas chromatography–mass spectrometry was used to identify any minor components found in each chemical. In many cases the minor components were stabilizers usually added to commercial formulations.

Animals and Conditions

Osborne-Mendel rats (Battelle Memorial Institute, Columbus, Ohio) were chosen because previous studies by FDA scientists (*1*) and by Reuber and Glover (*2*) had shown this strain was sensitive to various chlorinated compounds such as DDT or carbon tetrachloride. The B6C3F1 mouse, a hybrid of the C57B1/6 female and C3H/He male (Charles River, Wilmington, Massachusetts) was selected because of previous extensive use in NCI bioassays (*3*). The 35-day-old rats and 25 day-old-mice, as received from the suppliers, were quarantined for 10 days and randomly assigned to treatment groups. Rats were individually housed in wire mesh galvanized steel cages; mice in groups of 10 of one sex in polypropylene cages (fitted with filter bonnets) on Sanichips bedding. Cages for rats were changed weekly; for mice twice each week. The temperature range was 20–24°C; air was changed 10–15 times per hour, while relative humidity was kept in the 45 – 55% range. Feed (Wayne Lab-Blox meal) and water were freely available.

*Carcinogen Metabolism and Toxicology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014.

Acute Study

For each compound single dose range finding studies were done in two male rats and two female mice. Up to 10 individual dose levels in corn oil were given by gavage; the animals were then observed for 14 days. The lowest doses causing death were selected as the highest level for the 8-week subchronic study, the primary objective of which was to determine the maximum tolerated dose (MTD) for the chronic test. In the subchronic phase, six groups of five males and five females of each species were used. Five groups received the test compound at varying dosages; the remaining group received the corn oil vehicle only. Dosing was by gavage, 5 days weekly for 6 weeks. The weekly weights served as a guide for the dosage during the next week. After the 6-week dosing period, the animals were observed an additional 2 weeks to detect delayed toxicity and/or the rate of recovery. Animals were then killed and a gross necropsy was done to detect abnormalities.

Chronic Test

Based on the results of the subchronic study, two dose levels of each compound were chosen to be given to both sexes of Osborne-Mendel rats and B6C3F1 mice, in groups of 50 animals each, a total of 400 animals in eight groups. There were also 99 male and 98 female rats, 77 male and 80 female mice as untreated colony controls. Each compound as a corn-oil solution was administered by gavage under a hood for 5 consecutive days a week. Carbon tetrachloride was administered as a positive control compound.

The animal weights and food consumption per cage were obtained weekly for the first 10 weeks and monthly thereafter. Animals were checked daily for mortality. In cases where mortality was high or weight gain was lower than within 10% of the controls, the dose levels of a compound were reduced or dosing was on an intermittent schedule to allow survival. Generally dosing of the animals was stopped after 78 weeks. After an additional 12 weeks on observation or a total of 90 weeks, the mice were terminated; at 110 weeks the rats were killed. A gross necropsy was performed on each animal that died during the experiment or was killed at the end. Specified organs* plus any tissue containing visible lesions were fixed in 10% buffered formalin embedded in Paraplast, and sectioned at 5 μm for slides. Hematoxylin and eosin staining was used routinely, but other stains were employed when needed. Diagnoses of any tumors and other lesions were coded according to the Systematized Nomenclature of Pathology (SNOP) of the College of American Pathologists, 1965. Further information on the experiments is included in the individual report on each compound, as well as statistical analysis of the results.

*Brain, pituitary, adrenal, thyroid, parathyroid, trachea, esophagus, thymus, salivary gland, lymph nodes, heart, nasal passages, lung, spleen, liver, kidney, stomach, small intestine, large intestine, pancreas, urinary bladder, prostate or uterus, seminal vesicles and testis with epididymis or ovary, skin with mammary gland, muscle, nerve, bone, and bone marrow.

Results

Compounds

In some compounds small amounts of stabilizers or other minor impurities were detected, generally by gas chromatography. Details of the columns, oven temperature and the like are in the individual reports. As examples, for trichloroethylene the main impurity was 1,2-epoxybutane (0.19%) while in chloroform there was 2% of ethanol, added as a stabilizer. The 1,1,1-trichloroethane sample contained approximately 3% *p*-dioxane.

Animal Tests

Based on body weight gains and survival rates during the acute and subchronic studies, estimated maximum dose levels for each compound were selected (Table 1). In the chronic study, due to signs of toxicity in some of the groups, the doses were decreased in order to maintain the animals. Conversely, if there was no effect on weight gain, doses were increased. The report for each compound gives the details along with the time-weighted average dose.

Table 1. Maximum dose level (MTD) for oral intubation

	Level, mg/kg			
	Rat		Mouse	
Compound	Male	Female	Male	Female
Trichloroethylene	1000	1000	2400	1800
Chloroform	180	180	300	500
1,1,1-Trichloroethane	1500	1500	1500	1500
Iodoform	120	60	100	100
1,2-Dibromoethane	40	40	120	120
1,2-Dibromo-3-chloropropane	30	30	260	260
1,2-Dichloroethane	100	100	200	300
1,1-Dichloroethane	900	900	3000	3600
1,1,2-Trichloroethane	100	100	100	100
Hexachloroethane	500	500	500	500
3-Chloropropene	55	55	200	300
Tetrachloroethylene	1000	1000	1000	1000
Carbon tetrachloride	100	150	2500	2500

Data on the primary tumors at the main anatomical sites, in comparison with findings in controls, for each compound are provided in the tables.

Reports have been issued by the Carcinogenesis Program of NCI on three compounds, trichloroethylene, chloroform, and 1,1,1-trichloroethane (methylchloroform, (4–6). The first of these, trichloroethylene, had little or no effect in rats but hepatocellular carcinomas appeared in mice (Table 2).

As was expected, because of a previous study on chloroform (7), hepatocellular carcinomas occurred at a high incidence in both male and female mice given this compound. On the other hand, rats showed a different pattern. Kidney tumors were increased in males and thyroid tumors in females

Table 2. Occurrence of tumors from trichloroethylene.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Reticulum-cell sarcoma, lymphosarcoma, malignant lymphoma	Rat	0	0	0	1	1	1
Mammary fibroadenoma and adenocarcinoma		0	0	0	4	5	7
Hemangiosarcoma		1	1	2	0	1	0
Thyroid-follicular adenoma and adenocarcinoma		1	2	1	0	0	1
Pituitary-chromophobe adenoma		0	0	0	4	2	6
Metastases		2	0	0	0	0	0
Total tumors		7	8	5	10	14	16
Number of animals examined		20	50	50	20	48	50
Animals with tumors		5	7	5	7	12	12
Liver-hepatocellular carcinoma	Mouse	1	26	31	0	4	11
Reticulum-cell sarcoma, lymphosarcoma, malignant lymphoma		1	4	2	1	5	6
Carcinoma of lung or alveoli		0	0	1	0	2	2
Adenoma of lung		0	5	1	1	2	5
Metastases		0	4	11	0	0	0
Total tumors		5	41	51	4	19	24
Number of animals examined		20	50	48	20	50	47
Animals with tumors		5	30	33	4	14	19

Table 3. Occurrence of tumors from chloroform.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Hepatocellular carcinoma	Rat	0	0	1	0	0	0
Kidney-epithelial tumors		0	4	13	0	0	2
Thyroid tumors		4	3	4	1	8	10
Metastases		0	2	5	0	0	5
Total tumors		11	29	29	22	42	37
Number of animals examined		19	50	50	20	49	48
Animals with tumors		9	24	20	12	24	24
Liver-hepatocellular carcinoma	Mouse	1	19	44	0	36	39
Kidney-epithelial tumors		1	1	2	0	0	0
Metastases		0	2	4	3	0	2
Total tumors		4	31	58	6	46	42
Number of animals examined		18	50	45	20	46	41
Animals with tumors		4	26	44	2	37	39

(Table 3). Surprisingly, the analog 1,1,1-trichloroethane had no noticeable effect (Table 4) although the relatively poor survival of treated animals may have precluded any carcinogenic response. Still another chloroform analog, iodoform, had no significant action in mice. However, male rats at the lower dose level had a slight increase in thyroid tumors (Table 5). In any event, the renal action of chloroform did not hold for the iodo analog.

Table 4. Occurrence of tumors from 1,1,1-trichloroethane.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Liver-hepatocellular adenoma	Rat	0	0	0	0	0	1
Urinary bladder-transitional cell carcinoma		0	0	1	0	0	0
Pituitary adenoma		0	0	0	3	2	1
Adrenal adenoma and pheochromocytoma		1	3	1	2	3	2
Thyroid adenomas and carcinoma		0	0	0	3	0	1
Mammary adenoma and fibroadenoma		0	0	1	4	0	1
Mammary carcinoma		0	0	0	2	0	1
Metastases		0	0	0	0	0	1
Total tumors		3	6	5	14	7	5
Number of animals examined		20	49	50	20	50	50
Animals with tumors		3	6	5	7	7	4
Lung-adenoma	Mouse	1	1	1	0	0	1
Liver-hepatocellular adenoma and carcinoma		0	0	4	0	0	0
Malignant lymphoma		1	0	2	4	1	0
Metastases		1	0	2	3	0	0
Total tumors		4	2	6	4	2	3
Number of animals examined		15	47	49	18	48	50
Animals with tumors		2	2	5	3	2	3

Table 5. Occurrence of tumors from iodoform.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Pituitary adenoma and carcinoma	Rat	4	7	4	5	8	9
Adrenal tumors		1	0	0	0	0	1
Thyroid adenomas and carcinomas		1	11	5	2	5	2
Mammary fibromas or fibroadenoma		0	0	0	4	10	8
Mammary adenocarcinoma		0	1	1	1	6	4
Kidney tumors		0	0	0	1	0	0
Metastases		5	0	0	0	1	3
Total tumors		12	23	14	17	37	31
Number of animals examined		20	49	50	20	50	50
Animals with tumors		7	17	10	10	27	23
Lung adenomas and carcinomas	Mouse	1	4	4	1	1	0
Malignant histiocytic lymphoma		1	2	4	6	2	2
Liver—neoplastic nodule		1	0	0	0	0	0
Liver—hepatocellular carcinoma		2	5	7	1	1	0
Metastases		0	0	3	0	2	0
Total tumors		5	14	27	10	18	5
Number of animals examined		19	49	50	20	49	45
Animals with tumors		5	14	23	7	14	5

A preliminary note on the carcinogenicity of 1,2-dibromoethane and 1,2-dibromo-3-chloropropane (DBCP) has appeared (8). 1,2-Dibromoethane led to many squamous cell carcinomas of the stomach with numerous metastases in rats and mice (Table 6). In addition to causing stomach carcinomas with metastases in both rats and mice, DBCP also caused many mammary tumors in female rats at both dose levels (Table 7). However, the chloro analog of 1,2-dibromoethane, namely 1,2-dichloroethane, did not have quite such a potent effect. Some stomach tumors were present in male rats on the high dose level. Male mice showed some increase in hepatocellular carcinomas and both males and females on the high dose level had a definite increase in lung tumors (Table 8).

Table 6. Occurrence of tumors from 1,2-dibromoethane.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Stomach-squamous cell carcinoma	Rat	0	49	34	0	41	31
Hemangiosarcoma		0	4	2	0	1	1
Liver-hepatocellular carcinoma		0	0	0	0	1	5
Metastases		0	30	22	0	38	24
Total tumors		0	55	43	1	43	47
Number of animals examined		20	50	41	10	42	31
Animals with tumors		0	49	35	1	41	30
Stomach-squamous cell carcinoma and papilloma	Mouse	0	45	31	0	48	27
Liver-hepatocellular carcinoma		1	1	1	0	1	0
Metastases		0	146	126	0	159	62
Total tumors		2	49	36	0	57	34
Number of animals examined		19	49	48	20	49	50
Animals with tumors		2	45	31	0	48	29

Table 7. Occurrence of tumors from 1, 2-dibromo-3-chloropropane

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Stomach-squamous cell carcinomas and papillomas	Rat	0	48	48	0	39	38
Mammary carcinomas		0	1	1	0	24	30
Hemangiosarcoma		0	13	2	0	8	1
Metastases		0	87	105	0	29	29
Total tumors		1	78	61	4	78	71
Number of animals examined		20	50	50	20	50	50
Animals with tumors		1	49	47	4	44	43
Stomach-squamous cell carcinomas	Mouse	0	43	47	0	50	47
Liver-hepatocellular carcinoma		1	1	0	0	0	0
Metastases		0	110	88	0	141	88
Total tumors		2	45	48	0	51	53
Number of animals examined		19	45	50	20	50	47
Animals with tumors		2	43	47	0	50	47

A different structural analog or 1,1-dichloroethane showed practically no effect in rats and led to only a slight increase in liver tumors in male mice (Table 9). Addition of a second chlorine in the 2-position as in 1,1,2-trichloroethane, afforded a compound with little significant action in rats. How-

Table 8. Occurrence of tumors from 1, 2-dichloroethane.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Mammary adenocarcinoma	Rat	1	2	0	0	0	15
Mammary fibroadenoma		0	0	0	0	14	7
Pituitary adenoma		2	1	4	7	7	5
Hemangiosarcoma		0	12	5	0	5	5
Stomach-squamous cell carcinoma		0	2	9	0	1	0
Metastases		0	1	7	0	0	2
Total tumors		4	31	39	9	39	47
Number of animals examined		20	50	50	20	50	50
Animals with tumors		4	20	20	7	24	33
Liver-hepatocellular carcinoma	Mouse	1	6	12	1	0	1
Malignant histiocytic lymphoma		0	8	5	2	10	2
Lung-adenoma and carcinoma		0	1	15	1	7	16
Subcutaneous fibrosarcoma		0	0	4	0	0	0
Stomach-squamous cell carcinoma		1	1	2	0	2	5
Metastases		1	1	1	0	13	13
Total tumors		4	17	40	6	43	43
Number of animals examined		19	46	47	20	50	48
Animals with tumors		4	15	28	6	33	29

Table 9. Occurrence of tumors from 1, 1-dichloroethane.

Tumor	Species	Male			Female		
		Control	Low	High	Control	Low	High
Mammary adenomas	Rat	0	0	0	2	6	7
Mammary adenocarcinoma		1	0	0	0	1	5
Pituitary adenoma		1	0	2	2	6	4
Hemangiosarcoma		0	0	1	0	0	4
Metastases		0	5	0	0	1	2
Total tumors		9	6	7	4	17	26
Number of animals examined		20	50	50	19	50	50
Animals with tumors		6	6	5	4	12	18
Liver-hepatocellular carcinoma	Mouse	1	8	8	1	1	0
Stomach-squamous cell carcinoma or papilloma		1	1	0	1	0	0
Malignant histiocytic lymphoma		0	3	2	2	2	7
Subcutaneous fibrosarcoma		0	3	0	0	0	0
Kidney adenoma		0	3	0	0	0	0
Metastases		1	0	1	0	0	0
Total tumors		4	22	16	7	7	12
Number of animals examined		19	49	47	20	47	47
Animals with tumors		4	19	15	6	6	12

ever, both male and female mice had a decided increase in the number of hepatocellular carcinomas (Table 10). Addition of more chlorine atoms to the molecule afforded hexachloroethane which showed a like effect—minimal action in rats, liver tumors in mice (Table 11). Introduction of a double bond, as in 3-chloropropene, seemed to decrease the hepatomagenic action in mice. Rats were not affected significantly (Table 12).

Table 10. Occurrence of tumors from 1,1,2-trichloroethane.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Mammary fibroma and fibroadenoma	Rat	0	0	1	2	18	9
Mammary adenocarcinoma		1	1	1	0	0	4
Pituitary adenoma		1	5	1	2	9	5
Adrenal adenoma		0	0	1	0	3	1
Thyroid tumors		1	2	0	0	3	1
Hemangiosarcoma		0	4	1	0	1	0
Kidney-hamartoma		1	1	0	0	4	1
Metastases		0	1	0	0	0	4
Total tumors		9	26	14	4	50	28
Number of animals examined		20	50	50	19	50	50
Animals with tumors		6	21	11	4	34	22
Liver-hepatocellular carcinoma	Mouse	2	18	37	0	16	40
Lung adenoma and carcinoma		0	3	1	0	3	2
Malignant histiocytic lymphoma		2	7	1	4	4	1
Adrenal-pheochromocytoma		0	0	8	0	0	12
Stomach-squamous cell carcinoma and papilloma		0	2	1	0	0	1
Metastases		0	1	7	0	0	5
Total tumors		6	36	51	5	24	63
Number of animals examined		20	49	50	20	48	45
Animals with tumors		6	28	38	5	20	41

Table 11. Occurrence of tumors from hexachloroethane.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Pituitary adenoma and carcinoma	Rat	2	4	0	7	15	7
Adrenal tumors		1	2	0	2	1	1
Thyroid adenomas and carcinomas		2	3	6	2	5	4
Mammary fibromas and fibroadenomas		0	0	0	7	13	10
Mammary carcinoma		0	1	0	0	3	1
Kidney tumors		0	5	0	0	1	3
Metastases		4	3	0	1	1	1
Total tumors		13	22	12	22	50	27
Number of animals examined		20	49	50	20	50	49
Animals with tumors		9	17	11	14	33	20
Lung adenomas and carcinomas	Mouse	0	2	3	1	1	4
Malignant histiocytic lymphoma		0	0	0	4	9	7
Liver-hepatocellular carcinoma		3	15	29	2	20	15
Metastases		0	1	0	0	1	0
Total tumors		4	17	37	9	40	30
Number of animals examined		20	50	49	20	50	49
Animals with tumors		4	17	32	8	32	26

Tetrachloroethylene, an analog of trichoroethylene, led to similar results as trichloroethylene in animals. Liver tumors were increased in mice but there was no significant increase in rats (Table 13).

Table 12. Occurrence of tumors from 3-chloropropene.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Mammary fibromas and adenomas	Rat	0	0	0	7	13	4
Pituitary tumors		0	1	0	6	6	1
Adrenal-adenoma and carcinoma		1	1	0	2	0	0
Thyroid tumors		4	6	1	1	2	1
Hemangiosarcoma		2	2	2	0	3	1
Metastases		0	3	0	0	4	4
Total tumors		12	17	4	20	35	18
Number of animals examined		19	50	50	20	50	50
Animals with tumor		9	15	4	12	26	11
Liver-hepatocellular carcinoma	Mouse	2	8	1	0	1	1
Lung adenoma and adenocarcinoma		3	6	0	1	5	4
Malignant histiocytic lymphoma		1	2	2	1	6	7
Stomach-squamous cell carcinoma and papilloma		0	2	0	0	3	3
Metastases		0	5	0	0	3	0
Total tumors		6	24	3	4	20	17
Number of animals examined		20	45	49	19	48	44
Animals with tumor		5	19	3	4	18	15

Table 13. Occurrence of tumors from tetrachloroethylene.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Mammary adenoma and fibroadenoma	Rat	0	0	0	3	8	8
Mammary adenocarcinoma		0	0	0	1	1	2
Pituitary adenomas		0	1	0	4	9	6
Thyroid adenoma and carcinoma		1	0	1	0	0	2
Hemangiosarcoma		1	2	1	0	1	0
Metastases		2	0	0	0	7	2
Total tumors		7	5	6	10	25	27
Number of animals examined		20	49	50	20	50	50
Animals with tumors		5	5	5	7	17	15
Liver-hepatocellular carcinoma	Mouse	2	32	27	0	19	19
Malignant histiocytic lymphoma		2	0	0	4	0	1
Lung adenoma		0	3	0	0	0	1
Metastases		0	3	0	0	1	1
Total tumors		6	36	28	5	20	21
Number of animals examined		20	49	47	20	48	48
Animals with tumors		6	33	27	5	19	19

Table 14. Occurrence of tumors from carbon tetrachloride.

Tumor	Species	Males			Females		
		Control	Low	High	Control	Low	High
Mammary fibroma	Rat	0	0	0	4	4	3
Mammary adenocarcinoma		1	2	1	1	1	2
Pituitary tumors		4	5	1	5	7	2
Adrenal tumors		1	1	3	0	1	0
Thyroid-adenoma and carcinoma		1	1	1	2	2	4
Hemangiosarcoma		0	4	4	0	3	1
Liver-neoplastic nodule		0	9	3	1	11	9
Liver-hepatocellular carcinoma		0	2	2	1	4	2
Metastases		5	2	3	0	0	1
Total tumors		12	29	26	17	46	24
Number of animals examined		20	49	50	20	50	49
Animals with tumors		7	21	24	10	34	20
Liver-hepatocellular carcinoma	Mouse	3	49	47	1	40	43
Malignant histiocytic lymphoma		0	2	0	0	0	0
Adrenal adenoma and pheochromocytoma		0	28	28	0	15	10
Metastases		0	1	0	0	2	1
Total tumors		4	81	75	3	56	54
Number of animals examined		18	49	48	18	42	45
Animals with tumors		4	49	47	3	40	43

Carbon tetrachloride, used as a positive control, gave a high yield of hepatocellular carcinomas in male and female mice, as had been reported earlier (9). Also of interest was the increase in adrenal tumors in treated animals. Previous reports have not mentioned this type of tumor. In the rats, carbon tetrachloride caused neoplastic nodules and a few carcinomas of the liver. However, the incidence was lower than was anticipated (Table 14).

Discussion

From the results of these experiments, it is evident that oral administration of many halogenated aliphatics leads, in many cases, to hepatocellular carcinomas in mice and lesser effects in rats. Moreover, certain of the compounds such as 1,2-dibromoethane, DBCP, and chloroform had other unique carcinogenic actions in rats. It thus seems that such compounds could pose a hazard to humans on continued exposure. Of course, humans are more likely to receive these substances by inhalation, rather than by the oral route. Nevertheless, it seems prudent, in any environmental situation, to reduce exposure to such compounds to as low a level as is technologically feasible.

The experimental work reported was carried out at Hazleton Laboratories America, Inc., Vienna, Va., originally under contract NO1-CP-23278 with NCI, and currently under a subcontract to Tracor-Jitco, Inc.

The secretarial and technical assistance of Frances M. Williams and Joan Chase is appreciated.

REFERENCES

1. Fitzhugh, O. G., and Nelson, A. A. The chronic oral toxicity of DDT (2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane). J. Pharmacol. Exptl. Therap. 89: 18 (1947).
2. Reuber, M. D., and Glover, E. L. Cirrhosis and carcinoma of the liver in male rats given subcutaneous carbon tetrachloride. J. Nat. Cancer Inst. 44: 419 (1970).
3. Innes, J. R. M., et al. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. J. Nat. Cancer Inst. 42: 1101 (1969).
4. National Cancer Institute. Carcinogenesis Bioassay of Trichloroethylene. Carcinogenesis Technical Report Series No. 2, DHEW Publication No. (NIH) 76-802, U. S. Government Printing Office, Washington, D. C., 1976.
5. National Cancer Institute. Report on Carcinogenesis Bioassay of Chloroform. March 1, 1976.
6. National Cancer Institute. Bioassay of 1,1,1-Trichloroethane for Possible Carcinogenicity. Carcinogenesis Technical Report Series No. 3, DHEW Publication No. (NIH) 77-803, U. S. Government Printing Office, Washington, D. C., 1976.

7. Eschenbrenner, A. B. Induction of hepatomas in mice by repeated oral administration of chloroform, with observations on sex differences. J. Nat. Cancer Inst. 5: 251 (1945).
8. Olson, W. A., et al. Induction of stomach cancer in rats and mice by halogenated aliphatic fumigants. J. Nat. Cancer Inst. 51: 1993 (1973).
9. Eschenbrenner, A. B., and Miller, E. Liver necrosis and the induction of carbon tetrachloride hepatomas in strain A mice. J. Nat. Cancer Inst. 6: 325 (1946).